Review Article

Recent trends in traditionally used medicinal plants and drug discovery

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Abstract

The use of medicinal plants against diseases is an age-old practice which in recent times has caught the global attraction towards natural product drug discovery. Today, many modern drugs have originated in ethnopharmacology and traditional medicine. The identification of promising drug candidates, however, is a troublesome job that requires both classical and sophisticated modern screening methods. Many studies have devoted to understanding the basic principle and methods of drug discovery that can predict and eliminate the problematic molecules from further consideration. In this review, importance was given to outline the employment of modern tools and technologies towards discovering a novel drug. The relationship between experimental and computational approaches to the selection and optimization of bioactive compounds is also highlighted. This paper thus provides a brief perspective on the use of key drug design technologies, highlighting the opportunities and challenges of ethnopharmacological knowledge which can be an innovative and powerful discovery engine for newer, safer and affordable medicines.

***Keywords*:** Drug discovery, ethnomedicine, diseases

Introduction

Ethnopharmacology and natural product drug discovery remain a significant hope in the current research, lead-poor scenario. The use of plants as a source of basic medicine has its origin in ethnoveterinary practices which draw inspiration from traditional knowledge and is an important component of healthcare systems in India and world at large. WHO has estimated that up to 80% of the population in Africa and the majority of the populations in Asia and Latin America still use TM for their primary health care needs (WHO, 2002).The application of traditional medicine (TM) or ethnomedicine for the development and discovery of newer drugs, especially chasing for unusual plant-derived molecules with interesting and innovative mechanisms of action is the new challenge of modern healthcare today. Plants have been the basis of TM systems for thousands of years and continued to provide mankind with new remedies which have been documented by the ancient Chinese, Indian and African Civilisations (Taylor et al., 2001). Today, plant-derived drug discovery has become a hot topic of global importance, making a huge impact on both national and international health agendas and global trade as well. With rich source of phytochemicals plant kingdom provide relief against several health complications such as heart attack, cancer, diabetes, malaria, jaundice, wound healing, inflammation, bacterial and viral infections, helminthiases etc. throughout the world (Fabricant and Farnsworth, 2001; Stepek et al., 2007; Tandon et al., 2011). The interest in nature as a source of potential chemotherapeutic agents continues. With about 2.5lakh species of higher plants worldwide, till today less than 20% are scientifically studied and nearly 6% are screened for its pharmaceutical potential (Cronquist, 1988; Govaert, 2001; Verpoorte, 2001). Natural products and its derivatives share more than 50% of the drugs in the clinical world. Due to its easy accessibility, less cost of preparation and absence of undesirable side-effects, TM is increasingly solicited throughout the globe in the treatment of various infectious diseases and is the only affordable source of healthcare, especially for the world's poorest patients (Jabbar et al., 2005).

Ethnomedicine and drug discovery

Ethnomedicine may be defined broadly as the use of plants by humans as medicines (Farnsworth, 1994). The term "ethnobotany" was first used by Harshberger in 1896. He defined it as a study of plants used by the primitive and aboriginal people. Starting from Indian traditional medicine

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Table 1. Drugs derived from medicinal plants with their mode of action (Lahlou, 2013; Fabricant and Farnsworth, 2001)

Drugs	Action/Clinical Use	Plant Source
Acetyldigoxin	Cardiotonic	*Digitalis lanata* Ehrh.
Adoniside	Cardiotonic	*Adonis vernalis* L.
Aescin	Anti-inflammatory	*Aesculus hippocastanum* L.
Aesculetin	Antidysentery	*Fraxinus rhynchophylla* Hance
Agrimophol	Anthelmintic	*Agrimonia eupatoria* L.
Ajmalicine	Circulatory disorders	*Rauvolfia serpentina* (L.) Benth ex. Kurz
Allylisothiocyanate	Rubefacient	*Brassica nigra* (L.) Koch
Andrographolide	Bacillary dysentery	*Andrographis paniculata* Nees
Anisodamine, Anisodine	Anticholinergic	*Anisodus tanguticus* (Maxim.) Pascher
Arecoline	Anthelmintic	*Areca catechu* L.
Asiaticoside	Vulnerary	*Centella asiatica* (L.) Urban
Atropine	Anticholinergic	*Atropa belladonna* L.
Berberine	Bacillary dysentery	*Berberis vulgaris* L.
Bergenin	Antitussive	*Ardisia japonica* Bl.
Bromelain	Anti-inflammatory, proteolytic agent	*Ananas comosus* (L.) Merrill
Caffeine	CNS stimulant	*Camellia sinensis* (L.) Kuntze
(+)-Catechin	Haemostatic	*Potentilla fragaroides* L.
Chymopapain	Proteolytic, mucolytic	*Carica papaya* L.
Cocaine	Local anaesthetic	*Erythroxylum coca* Lamk.
Codeine	Analgesic, antitussive	*Papaver somniferum* L.
Colchicine	Antitumor agent, antigout	*Colchicum autumnale* L.
Convallotoxin	Cardiotonic	*Convallaria majalis* L.
Curcumin	Choleretic	*Curcuma longa* L.
Cynarin	Choleretic	*Cynara scolymus* L.
Deserpidine	Antihypertensive, tranqulizer	*Rauvolfia canescens* L.
Deslanoside, Digoxin	Cardiotonic	*Digitalis lanata* Ehrh.
Digitalin, Digitoxin, Gitalin	Cardiotonic	*Digitalis purpurea* L.
Etoposide, Teniposide	Antitumour agent	*Podophyllum peltatum* L.
Glaucaroubin	Amoebicide	*Simarouba glauca* DC.
Gossypol	Male contraceptive	*Gossypium* sp.
Hemsleyadin	Bacillary dysentery	*Helmsleya amabilis* Diels
Hyoscamine	Anticholinergic	*Hyoscamus niger* L.
Kainic Acid	Ascaricide	*Digenea simplex* (Wulf.) Agardh
Kawain	Tranquilizer	*Piper methysicum* Forst. f.
Khellin	Bronchodilator	*Ammi visnaga* (L.) Lamk.
Lanatosides A, B, C	Cardiotonic	*Digitalis lanata* Ehrh.
Lobeline	Smoking deterrent, respiratory stimulant	*Lobelia inflata* L.
Monocrotaline	Antitumor agent	*Crotolaria sessiliflora* L.
Morphine	Analgesic	*Papaver somniferum* L.
Neoandrographolide	Bacillary dysentery	*Andrographis paniculata* Nees
Noscapine	Antitussive	*Papaver somniferum* L.
Ouabain	Cardiotonic	*Strophanthus gratus* Baill.
Papain	Proteolytic, mucolytic	*Carica papaya* L.
Physostigmine	Cholinesterase inhibitor	*Physostigma venenosum* Balf.
Picrotoxin	Analeptic	*Anamirta cocculus* (L.) W. & A.
Pilocarpine	Parasympathomimetic	*Pilocarpus jaborandi* Holmes
Protoveratrines A & B	Antihypertensive	*Veratrum album* L.
Pseudoephedrine	Sympathomimetic	*Ephedra sinica* Stapf.
Quinine	Antimalarial	*Cinchona ledgeriana* Moens ex. Trimen
Quisqualic Acid	Anthelmintic	*Quisqualis indica* L.
Rescinnamine, Reserpine	Antihypertensive, tranqulizer	*Rauvolfia serpentina* (L.) Benth ex. Kurz
Rhomitoxin	Antihypertensive	*Rhododendron molle* G. Don
Rorifone	Antitussive	*Rorippa indica* (L.) Hochr.
Rotenone	Piscicide	*Lonchocarpus nicou* (Aubl.) DC.
Rotundine	Analgesic, sedative	*Stephania sinica* Diels
Salicin	Analgesic	*Salix alba* L.
Santonin	Ascaricide	*Artemisia maritima* L.
Scillarin A	Cardiotonic	*Urginea maritima* (L.) Baker
Scopolamine	Sedative	*Datura metel* L.
Silymarin	Antihepatotoxic	*Silybum marianum* (L.) Gaertn.
Strychnine	CNS stimulant	*Strychnosc nux-vomica* L.
Tetrahydropalmatine	Analgesic, sedative	*Corydalis ambigua* (Pallas) Cham. & Schltal
Theobromine	Diuretic, bronchodilator	*Theobroma cacao* L.
Theophylline	Diuretic; bronchodilator	*Camellia sinensis* (L.) Kuntze
Trichosanthin	Abortifacient	*Thymus vulgaris* L.
Tubocurarine	Skeletal muscle relaxant	*Chondodendron tomentosum* R. & P.
Valepotriates	Sedative	*Valeriana officinalis* L.
Vincamine	Cerebral stimulant	*Vinca minor* L.
Xanthotoxin	Leukoderma, vitiligo	*Ammi majus* L.
Yohimbine	Aphrodisiac	*Pausinystalia yohimbe* (K. Schum.) Pierre
Yuanhuacine	Abortifacient	*Daphne genkwa* Seib. & Zucc

"Ayurveda" – up to the development of sophisticated genetic engineering technologies, medical sciences has progressed to a newer height of its own. The 20th century revolutionized the thinking of drug use from traditional crude extract or semi-pure extract to the receptor theory of drug action. The idea of specific interactions of a drug molecule with biological macromolecules such as proteins or nucleic acids led scientists to the conclusion that individual chemical compounds present in the plant extracts, rather than some mystical "power of life" are the factors required for the biological activity of the drug. This lead to the beginning of a totally new era in pharmacology research, as pure, isolated chemicals, instead of extracts, became the standard treatments for diseases. Today, many bioactive compounds, responsible for the effects of crude extract, and their chemical structure is elucidated.

Despite remarkable progress in medical sciences and synthetic medicines, over 25% of worldwide prescribed drugs come directly or indirectly from plant source (Newman, 2000). Of the 252 drugs considered as basic and essential for healthy livelihood by WHO 11% are exclusively of plant origin and a significant number of synthetic drugs have their natural precursors. Today, drug discovery from medicinal plants mainly depends on biological activity guided isolation methods thereby leading to the isolation, identification and the discovery of important drugs. Table 1 showed the list of some of the important drugs and its source of medicinal plants.

During the last 40 years, several potent drugs have been derived from different plants: diosgenin from *Dioscorea* sp., reserpine and other anti-hypertensive and tranquilizing alkaloids from *Rauwolfia* sp., pilocarpine to treat glaucoma and dry mouth derived from a group of South American trees (*Pilocarpus* sp.), two powerful anti-cancer agents from the Rosy Periwinkle (*Catharanthus roseus*), laxative agents from *Cassia sp.* and as a cardiotonic agent to treat heart failure from *Digitalis* sp. The isolation of the anti-malarial drug, quinine in 1820 by the French pharmacists, Caventou and Pelletier from the bark of *Cinchona officinalis* which saves millions of lives today is well known. Similarly, serpentine isolated from the roots of *Rauwolfia serpentina* in 1953 was a revolutionary event in the treatment of hypertension and control of blood pressure. Vinblastine isolated from the *Catharanthus rosesus* is effective against Hodgkins, Choriocarcinoma, non-hodgkins lymphomas, leukemia, testicular and neck cancer (Farnsworth et al., 1967; Wagne and Wolff, 1977). Podophyllotoxin, a constituent of *Phodophyllum emodi* has the potential to cure testicular, small cell lung cancer and lymphomas. Recently several new plant-derived drugs that have been introduced to the U.S. market such as– artemether, a potent antimalarial artemisinin-derived drug isolated from *Artemisia annua*, galantamine isolated from *Galanthus woronowii* against Alzheimer's disease, nitisinone isolated from *Callistemon citrinus* against rare inherited disease tyrosinaemia, tiotropium isolated from *Atropa belladonna* against chronic obstructive pulmonary disease etc. (Van Agtmael et al., 1999; Graul et al., 2015; Frantz, 2004; Mundy and Kirkpatrick, 2004). Figure 1 showed some of the plants derived drugs.

Natural product chemistry and drug research

Plants contain a broad range of bioactive compounds such as lipids, phytochemicals, pharmaceutics, and several pigments. Pharmaceutically, extraction means the separation of a medicinally active portion of the plant or animal tissues from the inactive or inert components by using selective solvents in standard extraction procedures. The importance of most appropriate extraction methodology lies in the fact that when different methods are applied on the same plant material with the same solvent, the extraction efficiency varies significantly. In addition,

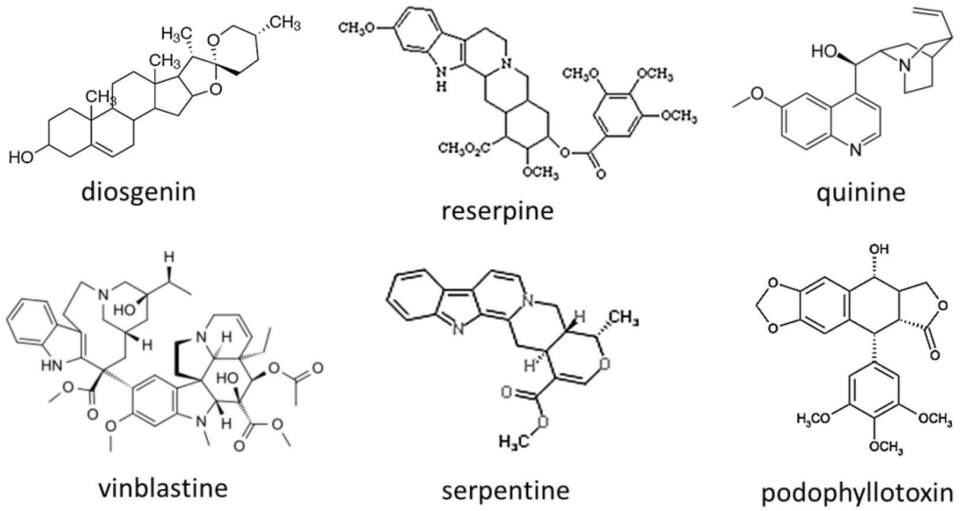

Figure 1. Phytochemicals of ethnobotanical origin

the method selected also needs to be standardized so as to achieve an acceptable degree of reproducibility. Numerous methods have been utilized to acquire compounds for drug discovery including isolation from plants and other natural sources, synthetic chemistry, combinatorial chemistry, and molecular modeling (Ley and Baxendele, 2002; Lombardino and Lowe, 2004). Despite the recent interest in molecular modeling, combinatorial chemistry, and other synthetic chemistry techniques by pharmaceutical companies and funding organizations, natural products, particularly medicinal plants, remains an important source of new drugs and new chemical entities (Butler, 2004).

A typical conventional phytochemical extraction process from plant material may contain the steps such as – collection, authentication, and drying of plant material, size reduction, extraction, filtration, concentration, drying, and reconstitution. The most common strategy used for the collection of medicinal plants is to explore the natural resources in folk medicine. Information on how the plants are used by an ethnic group is extremely important. The mode of formulation, dosages, oral or non-oral intake, the therapeutic property of use etc. must be known. However, the choice of a plant material screened for active compounds must meet the global and regional needs for efficient and safe drugs, while preserving the biodiversity and the environment on the other side. Once the authentication is done, the plant material must be dried and made into powder form using different mechanical tools. The objective of this size reduction is to rupture its organ, tissue and cell structures to increase the surface area of the plant cells so that its medicinal ingredients are exposed to the extraction solvent (Butler, 2004).

Plants also contain a range of secondary metabolites with different functional groups and polarities. Commonly encountered natural products include waxes, fatty acids, polyacetylenes, terpenoids (monoterpenoids, diterpenoids) steroids, essential oils (lower terpenoids, phenylpropanoids), phenolics (phenylpropanoids, flavonoids, anthocyanins, etc), alkaloids, and glycosidic derivatives. Several approaches can be employed to extract the plant material. *Solvent extraction* relies on the principle of either "liquid-liquid" or "solid-liquid" extraction. Although water is used as an extractant in many traditional protocols, organic solvents of varying polarities are generally selected in modern methods of extraction to exploit the various solubility of plant constituent. In a typical extraction protocol, the plant crude extracts were obtained drying the solvent by evaporating through the solvent evaporator. Once the extract has been obtained, the activity can be demonstrated by bioassay methods using both the crude extract or by using the fractionated extracts (Sarker et al., 2006; Handa et al., 2008).

Modern techniques for sample preparation from plants

A) Sonication-Assisted Extraction (SAE)

Sound waves, which have frequencies higher than 20 kHz, are mechanical vibrations in a solid, liquid and gas. The use of ultrasound in extraction process helps in recovering more plant extract by disrupting the biological cell wall and greater penetration of solvent into the cellular material (Mason et al., 1999). Simple, inexpensiveness, increased extraction yield, faster kinetics and improved the quality of extraction are the advantages of using SAE over other processes.

B) Microwave-Assisted Extraction (MAE)

Microwaves are electromagnetic radiations with a frequency from 0.3 to 300 GHz. MAE process includes extraction of high-value compounds from natural sources including phytonutrients, nutraceutical and functional food ingredients and pharmaceutical actives from biomass. MAE technology offers the following advantages: 1) improved products, increased purity of crude extracts, improved stability of marker compounds, possibility to use less toxic solvents; 2) reduced processing costs, increased recovery and purity of marker compounds, very fast extraction rates, reduced energy and solvent usage (Patil and Shettigar, 2010). By considering economical and practical aspects, MAE is a strong novel extraction technique for the extraction of nutraceuticals.

C) Accelerated Solvent Extraction (ASE)

Accelerated solvent extraction (ASE) is a solid-liquid extraction process performed at elevated temperatures, usually between 50ºC and 200ºC and at pressures between 10 MPa and 15 MPa. Extraction is carried out under pressure to maintain the solvent in its liquid state at high temperature. Increased temperature accelerates the extraction kinetics and elevated pressure keeps the solvent in the liquid state, thus achieving safe and rapid extraction (Kaufman and Christen, 2002).

D) Supercritical Fluid Extraction (SFE)

SFE is a one among the most technologically advanced extraction system. Supercritical state is achieved when the temperature and the pressure of a substance are raised over its critical value. The supercritical fluid has characteristics of both gases and liquids. Compared with liquid solvents, supercritical fluids have several major advantages: 1) the dissolving power of a supercritical fluid solvent depends on its density, which is highly adjustable by changing the pressure or/and temperature; 2) the supercritical fluid has a higher diffusion coefficient and lower viscosity and surface tension than liquid solvent, leading to more favorable mass transfer. In this method, CO_2 is used as a separating solvent. The advantages of SFE are the versatility it offers in pinpointing the constituents extract from a given material

and the end product left no solvent residues in it (Sihvonen et al., 1999; Wang and Weller, 2006).

E) Chromatographic techniques

The various chromatographic techniques used in natural product chemistry includes Preparative-HPLC, Liquid Chromatography-Mass Spectroscopy (LC-MS), Liquid Chromatography-Ultraviolet (LC-UV), Liquid Chromatography-Nuclear Magnetic Resonance (LC-NMR), Gas Chromatography-Mass Spectroscopy (GC-MS), LC-UV-MS, LC-UV-NMR, LC-UV-ES-MS (Oleszek and Marston, 2000; Philipson, 2007).

Genomics and proteomics in drug discovery

The growing knowledge of several diseases has shifted the traditional protocol of "one target, one drug" model to a new "multi-target, multi-drug" model that aim at systemic modulation of multiple targets (Hennings and Ilag, 2003). The evolution of drug discovery from chemistry-driven to biology-driven drug discovery was triggered by the realization that a better understanding of the genetic basis of diseases would ultimately lead to the formulation of more efficient drugs. After the completion of Human Genome Project, it has been believed that the genomic knowledge would be well enough for targeting novel drug target which was proved wrong in due course of time (Dror et al., 2009). Today, it has been realized that more than 95% of the 500 drugs in the market target proteins whereas DNA targeting drugs are found to be toxic because of less specificity (Lambert et al., 2007; Cseke et al., 2006).

Genomics deals with the studies of structures and functions of the genome and, in particular, genes. Proteomics, on the other hand, is the large scale study and analysis of protein structure and function. It is basically used to characterize differences in protein expression between normal and disease state biological specimens (Crul et al., 2000). In drug discovery pipeline, one of the first key steps is the identification of molecular targets. Genomics and proteomics are routinely used in today's drug discovery and development, in combination with combinatorial chemistry and high-throughput screening (Anderson and Seilhamer, 1997). Over the last two decades, the utilization of "omics" technologies have helped in identification and validation of drug targets, and design of more effective drugs thereby addressing the issues of target identification and lead candidate optimization (Walters et al., 1999). Various genomics technologies such as gene sequencing, statistical genetics, and gene expression analysis are used for the design and development of the drug. Many diseases develop as a result of a network of genes failing to perform correctly; pharmacogenomics can identify the genes which are involved in determining the responsiveness to a given drug. By knowing the target gene, the compound that works best overall against all its subtypes could be chosen and finally reduces the possibilities of emerging adverse side effects. For example, the gene-expression pattern for the liver of an animal administered a drug can indicate whether gene pathways related to toxicity have been turned on. The quest for new drug with genomic approach is limited if one doesn't go for its product, the proteins. Proteins are vital parts of living organisms, as a cell is dependent upon a multitude of metabolic and regulatory pathways for its survival (Drews, 2000). Several studies have shown that there is no strict relationship between genes and the protein complement or 'proteome' of a cell (Pandey and Mann, 2000; Lewis et al., 2000). Figure 2 shows the various target levels of various drugs developed today. Due to various levels of post-transcriptional regulation from mRNA to protein, a given gene may generate different products. Therefore, before designing a drug at the protein level, the expression profile of a gene and its regulation protocols must be explored.

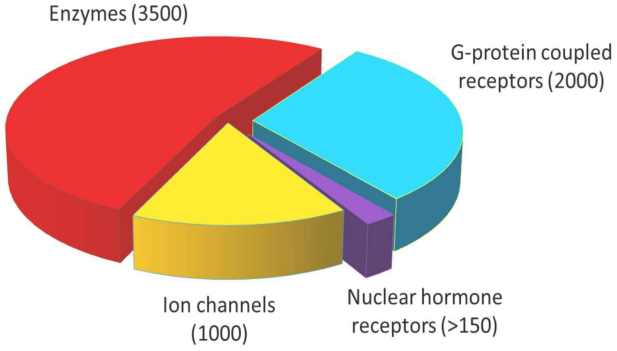

Figure 2. Predicted numbers of potential drug targets belonging to different biochemical classes (Lennon, 2000).

Computational drug discovery: *In-silico* approach

Drug discovery program typically starts with the identification of suitable drug targets, whereas lead discovery identifies novel chemical that acts on those targets. Such targets are biomolecules, proteins such as receptors, enzymes and ion channels. Although the initial steps of target validation are usually obtained *in-vitro* and in animal models the ultimate validation can be achieved only in clinical experiments in humans. In drug discovery, the so-called lead identification starts with the design and development of a suitable assay to monitor the target under study. Subsequently, high-throughput screening exposes the target to a large number of chemical compounds. Although most of the process of early pharmaceutical researchers relies predominantly on experimental work in the laboratory, today computer-aided drug design/discovery and computational methods have become increasingly important in drug discovery (Yoshida et al., 2001).

The human genome contains approximately 3% of the

3×10^9 bases that actually codes for proteins and identification of a gene, therefore, is still a difficult task (Terstappen and Reggiani, 2001). However, Expressed Sequence Tag (EST) databases represent an important source for target discovery that provides information about sequences of expressed genes. By knowing the level of expression of a particular gene in a given cell or tissue and comparing the expression level in normal and disease state, novel drug target molecule can be identified. Today several new *in-vitro* technologies for high-throughput gene-expression analysis have been developed including serial analysis of gene expression (SAGE), variants of differential display and DNA microarrays (gene chips), which can overcome the limits of EST-based approaches (Ryan et al., 2002). Another important use of *in-silico* research in drug discovery is the elucidation of gene function. Usually, a drug target is much more attractive if its function is known. The function of new and unknown target can be predicted by subjecting the sequences (DNA, RNA or amino acids) to similarity search and homologies to sequences of known function. However, diversity of compounds sometimes imposes difficulties in targeting a genuine and effective drug. *In-silico* (virtual) screening helps to identify the best possible ligand for a biological molecule by structure based combinatorial approach or pharmacophore modeling. In this approach lead compounds are generated from a large number of chemicals on the basis of similarity clustering, grid-like partitioning of chemical space and other chemical properties (Feng and Wang, 2003). Before the development of a compound into a drug, optimization must be carried out in terms of potency, selectivity, pharmacokinetics, and toxicology. Using an *in-silico* approach one can screen the mode of intake of a particular drug.

Computational drug discovery is an effective strategy for accelerating such drug discovery programs. Today, the applicability of computational drug discovery has been extended to nearly every stage of drug discovery including molecular docking; pharmacophore modeling and mapping, *de-novo* design, molecular similarity calculation and sequence-based virtual screening (Corcoran and Spraul, 2003). Figure 3 explains the various steps of pharmacology drug design pipeline. Molecular docking plays a central role in predicting protein–ligand interactions, which has been extensively used over the last few decades for drug hit discovery and lead optimization (Walter and Namchuk, 2003). In a research paper, Walters assumed so called 'rule of five' to predict a drug as orally bioactive if the *hydrogen bond donors*, *hydrogen acceptors*, *relative molecular weight,* and *lipophilicity* are less than *5*, *10*, *500* and *5*, respectively. Unfortunately, the *in-silico* approach can be applied when the 3D x-ray crystallographic structure of a particular biological molecule is known (Kitchen et al., 2005). Today most of the available x-ray crystallographic structures are enzymes

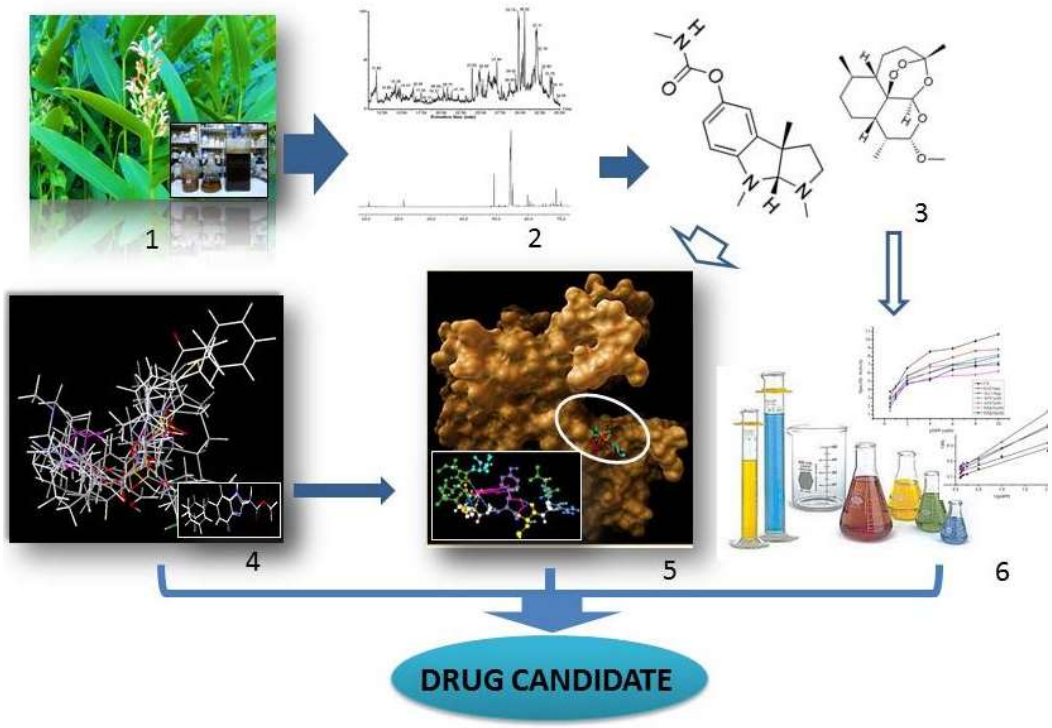

Figure 3. Steps of drug discovery process: (1) Target identification and selection, (2) Isolation and purification, (3) Structural identification and elucidation, (4) Lead optimization (pharmacophore) to improve potency, (5) Analyze structure for potential ligand binding, docking of small molecules using computational methods, (6) Biochemical assays, cytotoxicity, pharmacokinetics, toxicological studies etc.

because membrane proteins such as receptors and ion channels are exceedingly difficult to crystallize. This hurdle can be challenged, although not satisfactorily, by homology modeling. Some of the recent examples of successful applications of computational approach in drug discovery are: phytochemical from *Ceratostigmawill mottianum* effective against *Helicobacter pylori*, 6-gingerol as anticancer, torcetrapib as antihyperlipidemia etc. (Martin, 2005; Lewis et al., 2005). However, the big question – "whether *in-silico* approaches improve the identification of high-quality lead compounds and ultimately the delivery of new drugs to the market is yet to be explored".

High-throughput screening

The High-Throughput Screening (HTS) approach is regarded as the most powerful tool in drug discovery (Butler, 2005). It offers us to select a lead compound from large compound collections by identifying biologically active compounds. HTS approach work on "Key-Lock" principle to screen out lead compound with very high efficiency and productivity. Although the target-to-lead efforts in drug discovery generally take several years, HTS approach completes the same work within few weeks to months. The great power of HTS allows it to finish a search amongst one million compounds within 3 months, and this power contributes to speed up the new drug development in pharmaceutical industries. However, the HTS approach has its own problems. The pathogenesis of a disease requires the involvement of several pathways and a series of biological molecules, including hormones and receptors. Targeting at a single target, therefore, may not make a treatment efficient (Cai et al., 2006).

Future prospects and challenges in drug discovery

Plants have always been a source of inspiration and way of livelihood to human kind. Plant-derived and other natural products provided many novel bioactive molecules that are available in the market today. However, in the last several year's many pharmaceutical companies have either terminated or scaled down their natural products drug-discovery programs and focusing largely in favor of combinatorial chemistry which can generate libraries consisting of millions of compounds. Along with pharmaceutical companies, some biotechnology companies also work on lead identification from a natural product (Ahn and Wang, 2008). Many plant-derived drugs currently undergoing clinical trials are obtained by these emerging "biotech" companies. In the past, drug discovery was time-consuming and a difficult task. Nowadays, the speed of bioassay-guided fractionation has been improved significantly by improvements in instrumentation such as high-performance liquid chromatography (HPLC) coupled to mass spectrometry (MS)/MS, LC-MS), higher magnetic field-strength nuclear magnetic resonance (NMR) instruments, and robotics to automate high-through put bioassays. The introduction of capillary NMR (cap-NMR) spectroscopy is a recent major breakthrough for the characterization of compounds present in extremely small quantity (Sink et al., 2010; Trist, 2011). The high sensitivity of the cap-NMR probe allows combination of NMR spectroscopy with other analytical "hyphenated" techniques, such as LC-NMR-MS and LC-solid phase extraction (SPE)-NMR (Rouhi et al., 2003). A state-of-the-art integrated system for LC-NMR-MS and LC-SPE-NMR-MS has also been developed and the hardware can be switched from LC-NMR-MS to LC-SPE-NMR-MS with minimal reconfiguration empowering the efficiency and speed of compound isolation and drug discovery. LC-SPE-NMR in combination with HPLC-electrospray ionization mass spectrometry (ESIMS) has been used for the rapid identification of compounds present in crude extracts of plants (Ou-Yang et al., 2002). The development of automated high-throughput techniques has allowed rapid screening of plant extracts reducing the limitations of another biological assay. With the advances in data handling systems and robotics, large samples can be assayed in just one day or a week (Masoudi-Nejad et al., 2013). Similarly, the success of computational sciences in the field of drug design and discovery has given a new dimension to the pharmaceutical industry. Also, the HTS methods have been developed with computational filtering methods to identify and remove potentially problematic compounds that can give false-positive results (Sliwoski et al., 2013). In the future, the use of NMR "hyphenated" techniques are expected to allow quick "de-replication" (a process of eliminating known and active compounds in the plant extracts that have been studied previously), and also the HTS approach may permit the rapid identification of the active compounds. Moreover, for compounds that are uneconomical to synthesize, and only available in a very small quantity, use of plant cell cultures methods can be employed (Jeong et al., 2009). However, despite these successes in drug discovery, future endeavor face many challenges. On the other side, the persistence of highly endemic parasitic, bacterial and viral diseases makes human populations vulnerable to emerging and re-emerging diseases. Although there are adequate resources for the contemporary provision of synthetic and natural drugs, it would be false to presume that 20 or 30 years from now those resources will still be available. With the increasing use of medicinal plants, the future looks threatened by complacency concerning their conservation. Reserves of herbs and stocks of medicinal plants in developing countries are diminishing and in danger of extinction as a result of growing trade demands for cheaper healthcare

products and new plant-based therapeutic markets in preference to more expensive target-specific drugs and biopharmaceuticals. These concerns must be raised by scientific community both in national and international platforms so that the future remains safe to all the living organisms including human beings.

Conclusion

With the increasing interest and promising drug candidates in the current drug development pipeline along with the lessening of technical drawbacks associated with natural product research, there are better opportunities to explore the biological activity of previously inaccessible sources of natural products. In addition, the increasing acceptance of chemical diversity of natural products is well suited to provide the needs for future drugs and there will be further developments in the use of novel natural products and chemical libraries in drug discovery campaigns. However, since the vast proportion of the available higher plant species has not yet been screened for biologically property, drug discovery from plants still remains an essential component in the search for new medicines, particularly with the development of highly sensitive and versatile analytical methods. Expectations will remain high and only time will tell whether ethnomedicines lead the way forward towards a healthier world with healthier people.

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Conflict of interest

Author declares no conflict of interest.

References

Ahn NG, Wang AHJ. 2008. Proteomics and genomics: Perspectives on drug and target discovery. Current Openion in Chemical Biology, 12: 1-3.

Anderson NL, Seilhamer J. 1997. A comparison of selected mRNA and protein abundances in human liver. Electrophoresis, 18: 533-7.

Butler MS. 2004. The role of natural product chemistry in drug discovery. Journal of Natural Products, 7: 2141-53.

Butler MS. 2005. Natural products to drugs: natural product derived compounds in clinical trials. Natural Product Reports, 25: 475-516.

Cai J, Han C, Hu T, Zhang J, Wu D, Wang F, Liu Y, Ding J, Chen K, Yue J, Shen K, Jiang H. 2006. Peptide deformylase is a potential target for anti-*Helicobacter pylori* drugs: Reverse docking, enzymatic assay, and X-ray crystallography validation. Protein Science, 15: 2071-81.

Corcoran O, Spraul M. 2003. LC-NMR-MS in drug discovery. Drug Discovery Today, 8: 624-31.

Cronquist A. 1988. The evolution and classification of flowering plants, Bronx, New York, Botanical Garden.

Crul M, van Waardenburg RC, Beijnen JH, Schellens JH. 2000. DNA-based drug interactions of cisplatin. Cancer Treatment Reviews, 28: 291-303.

Cseke LJ, Kirakosyan A, Kaufman PB, Warber S, Duke JA, Brielmann LH. 2006. Natural Products from Plants, (2nd Edn.), CRC Press, Boca Raton, FL.

Drews J. 2000. Drug discovery: A historical perspective. Science, 287: 1960-4.

Dror O, Schneidman-Duhovny D, Inbar Y, Nussinov R, Wolfson HJ. 2009. A novel approach for efficient pharmacophore-based virtual screening: Method and Applications. Journal of Chemical Information and Modeling, 49: 2333-43.

Fabricant DS, Farnsworth NR. 2001. The value of plants used in traditional medicine for drug discovery. Environmental Health Perspectives, 109: 69-75.

Farnsworth NR, Blowster RN, Darmratoski D, Meer WA, Cammarati LV. 1967. Studies on Catharanthus alkaloids IV Evaluation by means of TLC and ceric ammonium sulphate spray reagent. Lloydia, 27: 302-14.

Farnsworth NR. 1994. Ethnopharmacology and drug development. Ciba Foundation Symposium, 185: 42-51.

Feng Y, Wang NJ. 2003. The new generation of drug discovery and its analytical technologies. Journal of Bioequivalence and Bioavailability, 5: e42.

Frantz S. 2005. 2004 approvals: the demise of the blockbuster. Nature Reviews Drug Discovery, 4: 93-4.

Govaert R. 2001. How many species of seed plants are there? Taxon, 50: 1085-90.

Graul AI, Cruces E, Stringer M. 2015. The year's new drugs and biologic, 2014: Part-I. Drugs Today (Barc), 51: 37-87.

Handa SS, Preet S, Khanuja S, Longo G, dev Dutta R. 2008. Extraction Technologies for Medicinal and Aromatic Plants, ICS-UNIDO, AREA Science Park Padriciano, Trieste, Italy.

Henning SW, Ilag LL. 2003. Functional proteomics in drug discovery. Drug Discovery World Spring.

Jabbar A, Akhtar MS, Muhammed G, Lateef M. 2005. Possible role of ethnoveterinary medicine in poverty reduction in Pakistan: use of botanical anthelmintics as an example. Journal of Agriculture and Social Sciences, 1: 187-95.

Jeong C, Bode AM, Pugliese A, Cho YY, Kim HG, Shim JH, Jeon YJ, Li H, Jiang H, Dong Z. 2009. [6]-Gingerol Suppresses Colon Cancer Growth by Targeting Leukotriene A4 Hydrolase. Cancer Research, 69: 5584-91.

Kaufmann B, Christen P. 2002. Recent extraction techniques for natural products: microwave-assisted extraction and pressurised solvent extraction. Phytochemical Analysis, 13: 105-13.

Kitchen BD, Stahura FL, Bajorath J. 2004. Computational techniques for diversity analysis and compound classification. Mini Reviews in Medicinal Chemistry, 4: 1029-35.

Lahlou M. 2013. The success of natural products in drug discovery. Pharmacology & Pharmacy, 4: 17-31.

Lambert M, Wolfender JL, Staerk D, Christensen SB, Hostettmann K, Jaroszewski JW. 2007. Identification of natural products using HPLC-SPE combined with CapNMR. Analytical Chemistry, 79: 727-35.

Lennon GG. 2000. High-throughput gene expression analysis for drug discovery. Drug Discovery Today, 5: 59-66.

Lewis RJ, Bernstein MA, Duncan SJ, Sleigh CJ. 2005. A comparison of capillary-scale LC–NMR with alternative techniques: spectroscopic and practical consideration. Magnetic Resonance in Chemistry, 43: 783-9.

Lewis S, Ashburner M, Reese MG. 2000. Annotating eukaryote genomes. Current Openion in Structural Biology, 10: 349-54.

Ley SV, Baxendale IR. 2002. New tools and concepts for modern organic synthesis. Nature Reviews Drug Discovery, 1: 573-86.

Lombardino JG, Lowe JA. 2004. The role of the medicinal chemist in drug discovery-then and now. Nature Reviews Drug Discovery, 3: 853-62.

Martin GE. 2005. Small-volume and high-sensitivity NMR Probes. Annual Reports on NMR Spectroscopy, 56: 1-96.

Mason TJ, Paniwnyk L, Lorimer JP. 1999. The uses of ultrasound in food technology. Ultrasonics Sonochemistry, 3: S253-60.

Masoudi-Nejad A, Mousavian Z, Bozorgmehr ZH. 2013. Drug-target and disease networks: polypharmacology in the post-genomic era. In Silico Pharmacology, 1: 17.

Mundy C, Kirkpatrick P. 2004. Fresh from the pipeline: Tiotropium bromide. Nature Reviews Drug Discovery, 3: 643-4.

Newman DJ, Cragg G, Snader KM. 2000. The influence of natural products upon drug discovery. Natural Product Reports, 17: 215-34.

Oleszek W, Marston A. 2000. Saponins in food, feedstuffs and medicinal plants. Kluwer Academic publishers, New York.

Ou-Yang S, Lu J, Kong X, Liang Z. 2002. Computational drug discovery. Acta Pharmacologica Sinica, 33: 1131-40.

Pandey A, Mann M. 2000. Proteomics to study genes and genomes. Nature, 405: 837-46.

Patil PS, Shettigar RJ. 2010. An advancement of analytical techniques in herbal research. Journal of Advanced Scientific Research, 1: 8-14.

Philipson JD. 2007. Phytochemistry and pharmacognosy. Phytochemistry, 68: 2960-72.

Rouhi AM. 2003. Rediscovering natural products. Chemical and Engineering News, 81: 77-8.

Ryan TE, Patterson SD. 2002. Proteomics: drug target discovery on an industrial scale. Trends in Biotechnology, 20: S45-51.

Sarker SD, Latif Z, Gray AI. 2006. Natural products isolation, (2nd edition), Humana Press Inc, Totowa, New Jersey.

Sihvonen M, Jarvenpaa E, Hietaniemi V, Huopalahti R. 1999. Advances in supercritical carbon dioxide technologies. Trends in Food Science and Technology, 10: 217-22.

Sink R, Gobec S, Pecar S, Zega A. 2010. False positives in the early stages of drug discovery. Current Medicinal Chemistry, 17: 4231-55.

Sliwoski G, Kothiwale S, Meiler J, Lowe EW. 2013. Computational methods in drug discovery. Pharmacological Reviews, 31: 334-95.

Stepek G, Lowe AE, Buttle DL, Duce IR, Behnke JM. 2007. The anthelmintic efficacy of plant derived cysteine proteinases against the rodent gastrointestinal nematode, *Heligmosomoides polygyrus*, *in vivo*. Parasitology, 134: 103-12.

Tandon V, Yadav A.K, Roy B, Das B. 2011. Phytochemicals as cure of worm infections in traditional medicine systems, In: Srivastava, U.C., Kumar, S. Emerging Trends in Zoology. Narendra Publishing House, New Delhi, pp 1-27.

Taylor JLS, Rabe T, McGaw LJ, Jager AK, Staden J. 2001. Towards the scientific validation of traditional medicinal plants. Plant Growth Regulation, 34: 23-37.

Terstappen GC, Reggiani A. 2001. In-silico research in drug

discovery. Trends Pharmacological Sciences, 22: 23-6.

Trist DG. 2011. Scientific process, pharmacology and drug discovery. Current Openion in Pharmacology, 11: 528-33.

Van Agtmael MA, Cheng-Qi S, Qing JX, Mull R, van Boxtel CJ. 1999. Multiple dose pharmacokinetics of artemether in Chinese patients with uncomplicated falciparum malaria. International Journal of Antimicrobial Agents 12: 151-5.

Verpoorte RJ. 2001. Pharmacognosy in the new millennium: Lead finding and Biotechnology. Journal of Pharmacy and Pharmacology, 52: 253-62.

Wagne H, Wolff P. 1977. New Natural products and plant drugs with pharmacological, biological and therapeutical activity, In: Proceedings of the First International Congress on Medicinal Plant Research (Section-A), September, 1976, University of Munich, Germany, pp 6-10.

Walters WP, Murcko AA, Murcko MA. 1999. Recognizing molecules with drug-like properties. Current Opinion in Chemical Biology, 3: 384-7.

Walters WP, Namchuk M. 2003. Designing screens: How to make your hits a hit. Nature Reviews Drug Discovery, 2: 259-66.

Wang L, Weller CL. 2006. Recent advances in extraction of nutraceuticals from plants. Trends in Food Science and Technology, 17: 300-12.

WHO. 2002. WHO Traditional Medicine Strategy 2002-2005.

Yoshida M, Loo JA, Lepleya RA. 2001. Proteomics as a tool in the pharmaceutical drug design process. Current Pharmaceutical Design, 7: 291-310.